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Glucocorticosteroids

The glucocorticosteroids represent one of the most widely used categories of drugs for the treatment of human disease. These agents have complex antiinflammatory and immunosuppressive effects that render them highly effective in the management of a broad spectrum of disorders in which inflammation is a major manifestation. The problem confronting the therapist in using these drugs lies not in their lack of efficacy, but rather in the appreciable morbidity and occasional mortality associated with their chronic use. Unfortunately many of the conditions in which the glucocorticosteroids are singularly effective tend to be chronic unrelenting pathologic processes that respond quite well to these drugs, but that exacerbate profoundly when discontinued.

The dermatologist is confronted with an array of inflammatory skin diseases, the manifestations of which are well controlled with glucocorticosteroids. The dermatologic therapist can use several methods in prescribing these agents, including topical application, intralesional infiltration, intramuscular injection, and systemic administration. The selection of a route of administration will depend on several factors, including the extent and severity of the disease and its known responsiveness to the agent employed. In this chapter, the pharmacology of the glucocorticosteroids is discussed primarily from the perspective of their use by dermatologists. Thus, the topical, intralesional, intramuscular, and systemic uses of these agents are discussed separately under clinical uses.

History The ability of the dermatologist to alter the natural history of inflammatory skin disease changed dramatically in the early 1950s with the introduction of topical corticosteroids. Before that time the treatment of cutaneous inflammation consisted largely of watchful waiting or the substitution of one

type of inflammatory response with another evoked by noxious agents of different sorts, both physical and chemical. Cortisone, which was first used systemically and found to be effective in a number of inflammatory processes, was then employed as a topical agent and found to be inactive; however, hydrocortisone, the 11-hydroxy derivative of cortisone, was then shown to be effective in a number of inflammatory dermatoses (1–4). In the mid-1950s newer fluorinated derivatives of these compounds were introduced that greatly enhanced their therapeutic potency and simultaneously reduced their mineralocorticoid effects (5).

Chemical Classes The glucocorticosteroids are all derivatives of a class of hormones secreted by the zona fasciculata of the adrenal cortex. The starting point for glucocorticosteroid synthesis is cholesterol, which is produced in the adrenal gland from acetate by a series of enzymatic reactions requiring the presence of acetate, coenzyme A, and a number of intermediates. Furthermore, previously synthesized cholesterol is also taken up from the plasma by the adrenal gland. The extent to which each source (intrinsic or extrinsic) contributes to cholesterol levels in the gland remains poorly understood. As shown in Fig. 4-1, cholesterol is converted into Δ^5-pregnenolone and then into progesterone, which can ultimately form cortisol (hydrocortisone). These reactions occur in the zona fasciculata of the adrenal cortex.

It is important to have a clear concept of the structural characteristics of the various hormones secreted by the adrenal cortex. The three major categories are shown in Fig. 4-2. The fundamental ring structure is a phenanthrene ring to which a cyclopentane group has been added, producing a structure with 17 carbons. The addition of methyl groups at positions 10 and 15 yields a sterane ring containing 19 carbons that, with the addition of a hydrogen at position 5, becomes an androstane moiety, the prototype of androgenic hormones such as testosterone and androstenedione. Removal of the methyl group at C-10 yields a C_{18} derivative, estrane, the prototype of estrogenic hormones. Addition of an ethyl group to the sterane ring at position 17 with a hydrogen at position 5, produces pregnane, the category in which the glucocorticosteroids are found.

Progesterone (pregn-4-ene-3,20-dione) is a pregnane (21-carbon steroid) that is converted from Δ^5-pregnenolone by an enzyme known as 3β-ol-dehydrogenase that hydroxylates the 3-keto group and a second enzyme Δ^5-3-oxosteroid isomerase that catalyzes the transition of the double bond at the 5–6 position to the 4–5 position. Progesterone is a pivotal point in the pathway for all hormone synthesis by the adrenal gland. The addition of hydroxy groups at the 17 and 21 positions of progesterone yields 11-deoxycortisol (pregn-4-ene-17, 17, 21-diol-3,20-dione). Finally, the insertion of a hydroxy group at position 11 yields cortisol (11,17,21-trihydroxypregn-4-ene-3,20-dione). This reaction is catalyzed by the enzyme 11-β-hydroxylase.

As shown in Fig. 4-3 the major structural determinants of glucocorticoid action are the cyclopentanophenanthrene ring of the pregnane type containing keto groups at positions 3 and 20, hydroxy groups at positions 11, 17, and 21, and a double bond at the 4–5 position. Substitutions at positions 6, 9, 16, and 17 can greatly influence the pharmacologic potency of these hormones.

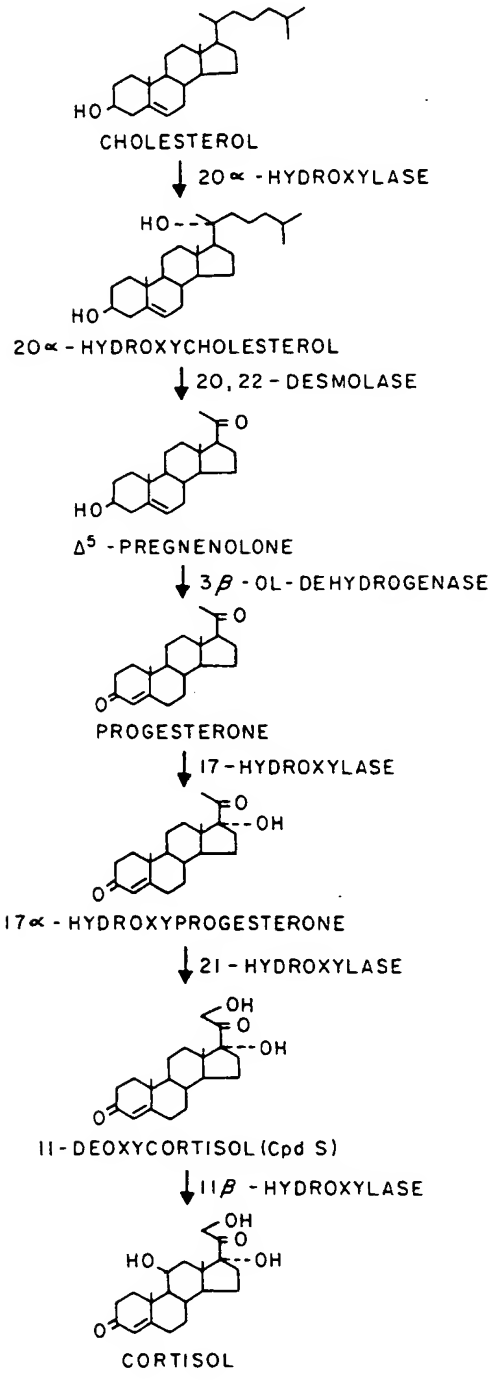

Figure 4-1 *Pathway of glucocorticosteroid synthesis.*

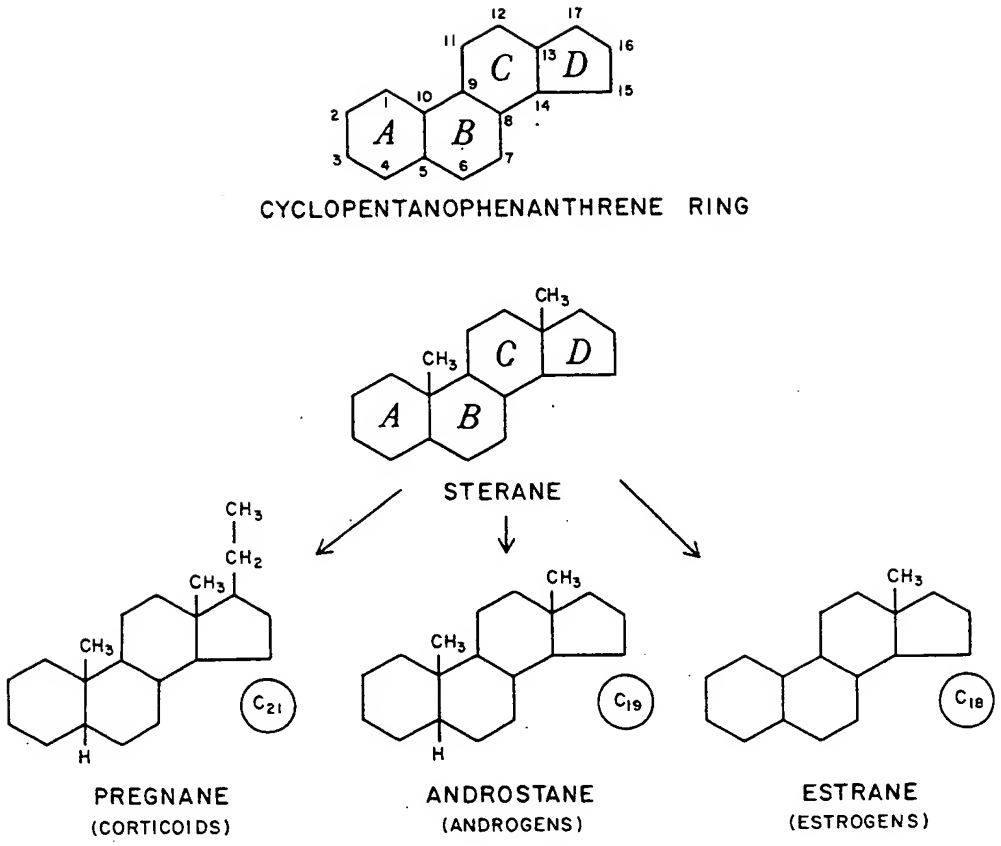

Figure 4-2 *The three major categories of steroid hormones are derived from a cyclopentanophenanthrene ring.*

The use of the term glucocorticosteroid is based on the ability of these substances, in physiologic quantities, to influence glucose homeostasis. This is accomplished through such biochemical effects as gluconeogenesis, the process whereby hepatic glucose is synthesized from amino acids derived from the breakdown of extrahepatic glucose, enhanced hepatic glycogen deposition, and elevation of blood glucose levels (6). The increased hepatic glucose synthesis is due in part to inhibition of peripheral protein synthesis and to direct enhancement of hepatic enzymes such as tyrosine aminotransferase and tryptophan pyrrolase (7). Thus, glucose synthesis occurs at the expense of protein catabolism, resulting in the atrophogenic effect of these hormones in various tissues manifested by osteoporosis, vascular fragility, and stria formation. These compounds also decrease glucose utilization by a peripheral antiinsulin action predisposing patients on high doses to the hyperglycemia and glycosuria of diabetes mellitus.

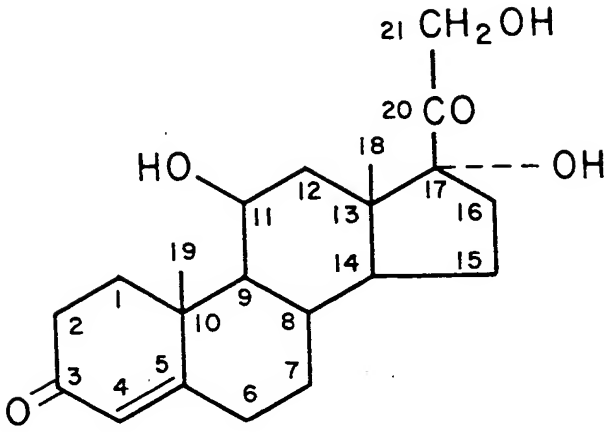

Figure 4-3 *Hydrocortisone. The major determinants of glucocorticosteroid effect are keto groups at positions 3 and 20, hydroxyl groups at positions 11, 17, and 21, and a double bond at the 4–5 position.*

The glucocorticosteroids have additional biologic actions that make them extremely useful when administered in pharmacologic doses. These actions include both antiinflammatory and immunosuppressive effects that are quite complex and that are closely linked to the protein-wasting actions of these hormones (8).

The antiinflammatory potency of the glucocorticoids is greatly amplified by insertion of a fluorine molecule in the 9α-position of cortisol. Addition of a 16α-hydroxyl group and a double bond in the 1,2 position yields triamcinolone, and conversion of the 16- and 17α-hydroxyls into the acetonide moiety yields triamcinolone acetonide, an exceptionally potent glucocorticosteroid (Fig. 4-4). It should be remembered that it is not the fundamental structure but rather the substitutions on it that become the major determinants of pharmacologic potency. For example, hydrocortisone or betamethasone have relatively low antiinflammatory effects but, with the addition of a valerate group, they become up to 300-fold more potent in this regard (9).

A multitude of different agents are available for topical and systemic therapy. The fundamental characteristics of the chemical structures of the more widely used therapeutic glucocorticosteroids are listed in Table 4-1. The substitutions listed refer to the numbers in Fig. 4-5.

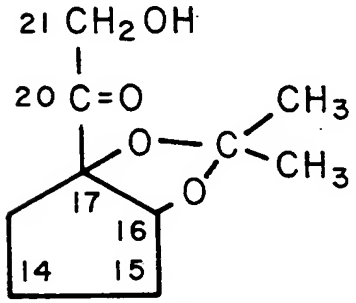

Figure 4-4 *Acetonide side-chain. The acetonide group greatly augments glucocorticosteroid effects.*

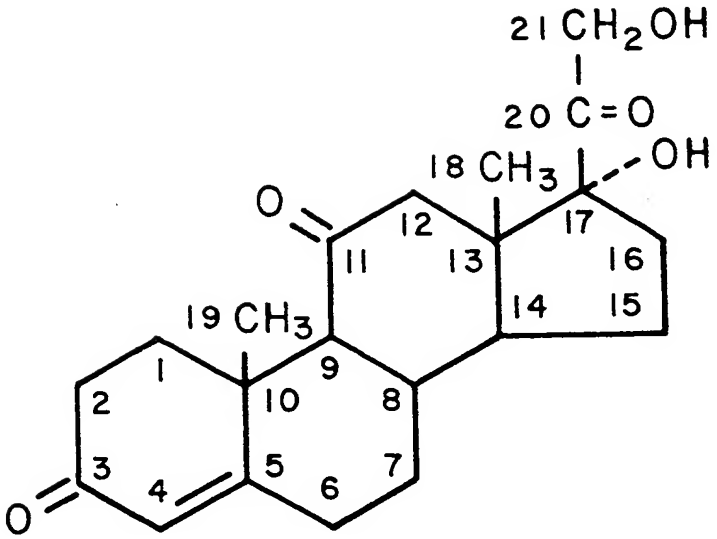

Figure 4-5 *The glucocorticosteroid molecule can be manipulated by substitution at various positions outlined in the text. (See Table 4-1.)*

Pharmacologic Actions

ANTIINFLAMMATORY EFFECTS Glucocorticosteroids are known to inhibit the release of lysosomal enzymes both in a variety of experimental systems and in human skin (10). Weissman and Fell (11) showed that the addition of hydrocortisone to normal fetal rat skin in culture enhanced its rate of differentiation. Furthermore, the corticosteroid largely prevented the severe necrosis in epidermis and dermis caused by ultraviolet radiation; it was suggested that this protective effect was due to a stabilizing action of the hormone on lysosomes to prevent the release of proteolytic enzymes. These hormones can also retard the redistribution of lysosomal hydrolases within the cell after certain types of toxic injury. As pointed out by Weissman, it is important to be aware that different steroid hormones may have rather contrasting effects on membranes (12). It has been proposed that steroids can be arranged on a linear scale relating their effects on isolated lysosomes to those on synthetic phospholipid–cholesterol liposomes (13). At one extreme are glucocorticosteroids, which diminish the release of enzymes from lysosomes, and at the other extreme are hormones with 5 β-H substitution, such as etiocholanolone and progesterone, which can labilize lipid-rich membranes.

Glucocorticosteroids also have major effects on circulating cells that mediate inflammatory responses. In experimental animals it is known that high doses of corticosteroids are lympholytic causing loss of circulating lymphocytes as well as diminution of the thymus gland (14). In humans, high daily doses of glucocorticosteroids have inhibitory effects on certain T-lymphocyte

Table 4-1 / Structural Characteristics of the More Widely Used Therapeutic Corticosteroids

Drug (Generic Name)	*Substitution and Position*
Betamethasone	1,2-Double bond 9α-Fluorine 16β-Methyl
Betamethasone benzoate	1,2-Double bond 9α-Fluorine 16β-Methyl 17α-Benzoate
Betamethasone dipropionate	1,2-Double bond 9α-Fluorine 16β-Methyl 17α-Dipropionate
Betamethasone valerate	1,2-Double bond 9α-Fluorine 16β-Methyl 17α-Valerate
Desonide	1,2-Double Bond 16,17α-Acetonide
Desoximethasone	1,2-Double bond 9α-Fluorine 16α-Methyl 17α-Desoxy
Dexamethasone	1,2-Double bond 9α-Fluorine 16α-Methyl
Diflorosone diacetate	1,2-Double bond 6,9α-Fluorine 16β-Methyl 17α-Acetyl 21 -Acetyl
Fluandrenolide	6α-Fluorine 16,16α-Acetonide
Flumethasone pivalate	1,2-Double bond 6,9α-Fluorine 16α-Methyl 21 -Acetyl
Fluocinolone acetonide	1,2-Double bond 6,9α-Fluorine 16,17α-Acetonide
Fluocinonide	1,2-Double bond 6,9α-Fluorine 16,17α-Acetonide 21 -Acetyl

(Continued)

Table 4-1 / Structural Characteristics of the More Widely Used Therapeutic Corticosteroids *(Continued.)*

Drug (Generic Name)	*Substitution and Position*
Halcinonide	9α-Fluorine
	16,17α-Acetonide
Hydrocortisone acetate	21 -Acetyl
Hydrocortisone valerate	17α-Valerate
Prednisolone	1,2-Double bond
Prednisone	1,2-Double bond
	11-Keto
Triamcinolone	1,2-Double bond
	9α-Fluorine
	16α-Hydroxyl
Triamcinolone acetonide	1,2-Double bond
	9α-Fluorine
	16,17α-Acetonide

functions, particularly the ability of these cells to respond to antigens such as tuberculin and allogeneic cells and to mitogens such as phytohemagglutinin (PHA) by blastogenesis and lymphokine release (15–17). B-lymphocyte function is also appreciably influenced by corticosteroids. Antibody production *in vitro* and *in vivo* as well as the capacity of antibody to evoke an inflammatory reaction are all inhibited by high doses of these drugs which are generally not used in treating patients (18–20). Mononuclear phagocytes are greatly affected by corticosteroids, which deplete circulating monocytes and tissue macrophages (21). Furthermore, corticosteroids can inhibit the stimulation of macrophages by activated T cells, immune complexes, and complement components (22). The responsiveness of macrophages to chemotactic factors and to lymphokines is diminished by glucocorticosteriods. Corticosteroids can also inhibit the secretion of neutral proteases and plasminogen activator by activated macrophages (23).

Others have suggested that the antiinflammatory effects of corticosteroids *in vivo* may largely reflect their ability to cause redistribution of circulating cells, including lymphocytes and neutrophils, rather than by directly inhibiting their functional activity (24). Thus, high doses of corticosteroids evoke transient decreases in circulating lymphocytes, monocytes, and eosinophils and increase the number of circulating polymorphonuclear leukocytes (PMNs) (25). The neutrophilic leukocytosis develops somewhat more rapidly than does the decrease in the other circulating cells (26). The elevated peripheral blood neutrophil count can be explained by two concomitant effects: enhanced re-

lease from the bone marrow and decreased movement from the bloodstream to sites of tissue inflammation (27). It is fair to say that the primary antiinflammatory effect of pharmacologic doses of glucocorticosteroids is to suppress the accumulation of cells at sites of tissue inflammation rather than to inhibit their function directly (28). This may be due to a drug-related suppression of adherence of neutrophils to endothelial cells (29). Phagocytosis, bactericidal function, and chemotaxis are all largely unaffected *in vitro* using doses of drug that are achievable *in vivo* (30). It is known that glucocorticosteroids produce monocytopenia and reduce the bactericidal activity of these cells (31).

Glucocorticosteroids have profound effects on circulating lymphocytes. Studies in experimental animals have shown major species differences in the susceptibility of lymphocytes to the lympholytic effect of glucocorticosteroids (32). Lymphocytes from humans, monkeys, and guinea pigs are largely resistant to the lympholysis that occurs in mice, rats, and rabbits; thus the lymphocytopenia that accompanies glucocorticosteroid administration in humans is not due to cell lysis and death. Rather, it seems clear that this effect occurs as a result of redistribution of circulating lymphocytes to other body compartments, particularly the bone marrow (33,34).

There appear to be at least two intravascular pools of lymphocytes, known as the recirculating and nonrecirculating pools. The recirculating population of cells comprises two-thirds of all intravascular lymphocytes. These cells move freely in and out of the vascular tree and can admix with the vast total body population of lymphocytes (35). The nonrecirculating pool of lymphocytes remains within the vascular tree and has a relatively short half-life. Glucocorticosteroids evoke a lymphocytopenia that occurs within 4 hours of drug administration and is due predominantly, if not exclusively, to a transient depletion of the recirculating lymphocyte pool (37). Within 24 hours the cell distribution returns to normal.

Glucorticosteroids also have inhibitory effects on macrophage function. It has been shown that these drugs can both inhibit macrophage responsiveness to chemotactic factors and depress their bactericidal and fungicidal activity *in vitro* (37).

IMMUNOSUPPRESSIVE EFFECTS The immunosuppressive effects of corticosteroids are expressed in both the immediate (antibody-mediated) and the delayed (cell-mediated) forms of hypersensitivity. The suppressive effects of corticosteroids on immunoglobulin synthesis are poorly understood, whereas much greater information is available concerning the effects of these agents on delayed hypersensitivity. For example, parenteral corticosteroids in high doses can reduce skin responsiveness to delayed antigens primarily by diminishing the recruitment of macrophages required for the expression of cell-mediated reactions or by interfering with antigen processing by these cells (38,39).

There is some specificity in this latter effect, since soluble antigens, such as tuberculin, are scarcely affected, whereas particulate ones, such as red blood cells, are greatly inhibited.

Coincident with the transient lymphocytopenia evoked by corticosteroids there is a relative loss of circulating T cells, leading to a decrease in the ratio of T cells to B cells. It is generally thought that corticosteroids have a greater inhibitory effect on T-cell as opposed to B-cell functions. Human T lymphocytes obtained 4 hours after treatment with corticosteroids lose T-suppressor activity, whereas T-helper activity is unchanged (19). B cells obtained after treatment with the corticosteroids could only synthesize 25 percent of the immunoglobulin made by cells before treatment. These differential effects of corticosteroids on T-suppressor cells, T-helper cells, and B cells may relate to differential inhibition of DNA synthesis and/or to membrane effects (19).

Also coincident with the transient lymphocytopenia evoked by corticosteroids is a differential decrease in the response of these cells to mitogens. Thus, *in vitro* responses to PHA are unaltered, but responses to pokeweed mitogen (PWM) and to concanavalin A (con A) are diminished, indicating a depletion of specific subsets of circulating lymphocytes. These data relate to the observations cited earlier indicating that corticosteroids inhibit human suppressor T-lymphocyte function, diminish B-lymphocyte responsiveness, and have little effect on helper T-lymphocyte function.

Other studies have shown differences between the immunosuppressive effects of acute versus chronic administration of corticosteroids. Thus lymphocytes remaining in the circulation after acute administration of these agents have intact functional responses to antigens and mitogens, whereas chronic administration causes suppression of antigen-induced lymphocyte functions and elaboration of macrophage migratory inhibitory factor (MIF), but has no effect on mitogen-induced proliferative responses (40). This differential effect is likely due to selective sequestration of certain lymphocyte subpopulations rather than to suppression of the functional capacities of the lymphocytes.

Corticosteroids can also inhibit antigen-induced lymphocyte function including *in vitro* proliferation and lymphokine synthesis and the interaction of effector molecules with their target cells (41). These drugs also block interleukin-1 production by antigen—presenting macrophages and interleukin-2 production by T-cells.

After activation by antigens or by mitogens, T lymphocytes secrete a series of soluble substances essential to the expression of cell-mediated immunity. These substances include macrophage MIF, macrophage aggregating factor (MAF), monocyte chemotactic factor, skin-reactive factor, and lymphotoxin. There is experimental evidence to show that corticosteroids do not affect the secretion of these substances by the T lymphocyte, but rather that they interfere with the interaction of these mediators with their target cells

(24). Therefore, it can be stated that the pharmacologic effect of corticosteroids on T-lymphocyte function is negligible; rather, these drugs interfere with the effects of the soluble mediators elaborated by these cells, which are important for recruiting other cells essential for the expression of delayed immune responses.

Finally, recent skin studies have shown that the topical application of corticosteroids in an *in vitro* microchemotaxis assay system causes significant inhibition of monocyte chemotaxis, but has little effect on neutrophil chemotaxis (42). These studies show that local inhibition of chemotaxis is an important antiinflammatory effect of corticosteroids, which can have different effects on monocytes and neutrophils.

DNA SYNTHESIS Topically applied corticosteroids can inhibit epidermal mitosis and DNA synthesis within 30 hours of a single topical application (43, 44). When the drug is applied repeatedly this effect is followed within several days by a rebound increase in DNA synthesis over control levels, illustrating the so-called tachyphylaxis that occurs in the skin after the topical application of corticosteroids (45,46).

VASOCONSTRICTION The vasoconstrictor effect in skin of topically applied corticosteroids has been widely used as an *in vivo* bioassay procedure to evaluate the relative antiinflammatory potency and the percutaneous absorption of these agents (47–49). This technique has clearly shown that the drug as well as the vehicle are important determining factors of the degree of percutaneous absorption (50). Furthermore, such studies indicate that a reservoir of drug remains in the stratum corneum for several days after cessation of topical application of corticosteroids under cellophane occlusion (51).

Corticosteroids have antianabolic effects in many tissues, among them the skin. Intradermal injection of corticosteroids in rats produces a dose-dependent, selective inhibition of tissue collagen nascent chain synthesis relative to noncollagen protein synthesis (52). Furthermore, a decrease in prolyl hydroxylase and lysyl hydroxylase activity occurs as well. Since the extent of hydroxylation of proline residues of collagen is directly related to the structural stability of the molecule, it is likely that these pharmacologic effects could mediate the atrophic changes seen in the skin of patients being treated with topical or systemic corticosteroids.

Metabolism and Kinetics The therapeutic potency of systemic corticosteroids is dependent on their relative intrinsic biologic potency and their relative rates of disappearance from the plasma (53). The intensity and duration of action of the drug determine its potency. Unfortunately, very little is known about the pharmacokinetics of corticosteroids administered either topically or

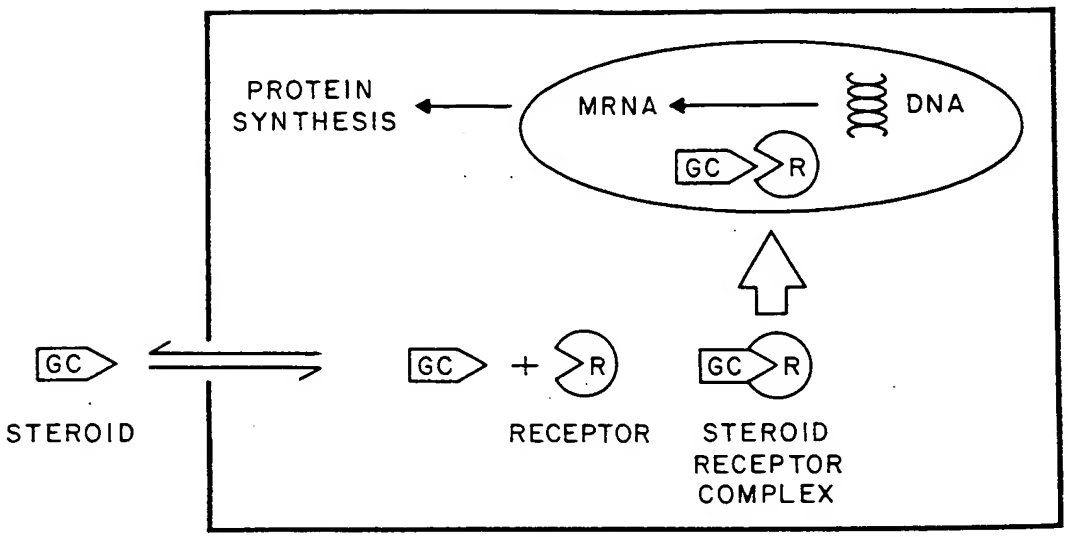

Figure 4-6 *Steroid–hormone-receptor concept.*

systemically. It is known that certain biologic effects of corticosteroids persist long beyond the disappearance of the drugs from the plasma. Whether the drug persists in the target tissue for prolonged periods or whether there is recovery from the biologic effect despite continuing presence of drug remains unknown.

The variability in the therapeutic efficacy and susceptibility to toxic side effects of these drugs suggest that there may be individual differences in rates of disapperance of the corticosteroids from the plasma. It has been shown that an increased or decreased metabolic clearance rate of dexamethasone is associated with a decreased or increased biologic effect of the drug (54). Furthermore, the side effects of corticosteroid therapy such as hirsutism and truncal and facial obesity can be correlated with slower rates of catabolism of prednisolone (55). Interestingly, however, therapeutic response does not correlate with the rate of catabolism of the drug.

It should also be emphasized that the concomitant administration of other drugs can alter the metabolism of corticosteroids. Phenobarbital has been shown to cause a 44 percent decrease in plasma half-life and an 88 percent increase in metabolic clearance rate of dexamethasone in asthmatic patients (56).

One major determinant of the biologic effectiveness of these agents appears to be the extent to which the drug can bind to cellular receptors for corticosteroids. Such receptors have been identified in the cytoplasm of cells in steroid-responsive tissues (Fig. 4-6) (57). The hormone receptor–steroid complexes then bind to nuclei and stimulate the production of mRNA, followed by the synthesis of specific proteins that may then evoke a biologic response.

One such protein is lipomodulin which inhibits phospholipase A_2 activity and thus impairs the release of membrane-bound arachidonic acid. Such receptors have been identified in epidermis and dermis of newborn mice and in normal adult epidermis. Further studies have shown that there is no direct correlation between the affinity of a corticosteroid for its epidermal receptor and its therapeutic efficacy. It remains unclear whether such receptor binding is in any way related to the antiinflammatory effects of topically applied corticosteroids. It is of interest that resistance to the tissue effects of cortisol has been correlated with reduced affinity of the glucocorticosteroid receptor for dexamethasone as well as with a diminished number of hormone receptors in studies performed in at least one human family with resistance to cortisol (57).

Clinical Use

TOPICAL Topically applied corticosteroids are used in a broad spectrum of inflammatory disorders. The diseases for which these agents are used have been characterized according to general responsiveness. Representative examples of dermatologic disorders that are responsive or relatively nonresponsive to these agents when used topically are listed in Table 4-2. It is generally believed that corticosteroids must be reapplied at frequent intervals (3–4 times daily) to obtain optimal therapeutic effects in most patients. However, it is known that topically applied corticosteroids form a reservoir in the stratum corneum that is slowly released (51). Furthermore, the repeated application of a corticosteroid to the skin evokes a tachyphylaxis-like response that cannot be negated even with intermittent (alternate-day) application insofar as inhibition of epidermal DNA synthesis is concerned (46). This raises the question of whether there is enhanced efficacy with multiple application of these drugs. Selection of the vehicle is another important consideration (58). In general,

Table 4-2 / Responsiveness of Dermatologic Disorders to Topical Corticosteroids

Relatively Responsive	*Relatively nonresponsive*
Atopic dermatitis	Pemphigus
Psoriasis	Pemphigoid
Eczematous dermatitis	Dermatitis herpetiformis
Contact dermatitis (chronic phase)	Herpes gestationis
Irritant	Epidermolysis bullosa
Allergic	Porphyria cutanea tarda
Seborrheic Dermatitis	Lupus erythematosus
Stasis dermatitis	Palmoplantar pustulosis
	Noninfectious granulomas

ointment bases provide greater occlusiveness, hence better penetration of these compounds. This likely results in greater vasoconstrictor effects of the corticosteroid as compared with its incorporation in other vehicles (59).

The solubility of a corticosteroid in its vehicle is also a major determinant of biologic effect, since the transfer of the drug from the vehicle into the skin occurs much more rapidly when the drug is in solution (60). Gels are vehicles in which solubility of the corticosteroids can be quite high; studies have shown that the vasoconstrictor effect of an agent in a gel can match that in an ointment base (50). The more important considerations in regard to vehicles and topical corticosteroids have been summarized (58–61).

There are some practical points to remember in selecting a topical corticosteroid for therapy. In general, ointments are preferable for disorders in which scaling and xerosis are a predominant feature, since these vehicles will help hydrate the stratum corneum. Creams are more useful in treating eczematous processes. Lotions and solutions are essential for hairy areas such as the scalp and the pubic region. It is also important to discuss this choice with the patient, since individual preferences should be given careful consideration. An incredible array of agents in different vehicles is available to the clinician. Most of the agents currently available in the United States are listed in Tables 4-3 through 4-5.

Topical therapy is highly inefficient because of the remarkable impenetrability of the stratum corneum. It is estimated that only 1 percent or less of an epicutaneously applied corticosteroid will be absorbed into the epidermis (62,63) (Fig. 4-7). Variations in therapeutic efficacy and biologic effect are likely the result of differences in intrinsic potency of the compound rather than the result of differences in percutaneous absorption.

The relative inefficiency of topically applied corticosteroids requires that

Table 4-3 / Low-Potency Topical Glucocorticosteroids[a,b]

Trade Name	*Generic Name*	*Dosage Forms and Concentration*
Hytone	Hydrocortisone	Spray, liquid, cream, ointment in
Synacort	Hydrocortisone	concentrations ranging from 0.25 to 2.5%
Celestone	Betamethasone	Cream, 0.2%
Decaderm	Dexamethasone	Cream, 0.1%
Decaspray	Dexamethasone	Spray, 0.2%
Hexadrol	Dexamethasone	Cream, 0.04%
Medrol	Methylprednisolone acetate	Ointment, 0.25%; 1.0%
Meti-derm	Prednisolone	Cream, 0.5%

[a]Currently available in the United States.
[b]Estimated cost to the patient: 7–10¢ per gram.

Table 4-4 / Medium-Potency Topical Glucocorticosteroids[a,b]

Trade Name	Generic Name	Dosages Forms and Concentration
Aristocort	Triamcinolone acetonide	Cream, 0.025%; 0.1%; ointment, 0.1%;
Benisone	Betamethasone benzoate	Gel, 0.025%; cream, 0.025%;
Cloderm	Clocortolone pivalate	Cream, 0.1%;
Cordran	Flurandrenolide	Lotion, 0.05%; cream, 0.025%; 0.05%; ointment, 0.025%; 0.05%: tape 4 ug/cm^2
Fluonid	Fluocinolone acetonide	Solution, 0.01%; cream, 0.01%; 0.025% Ointment, 0.025%
Halog	Halcinonide	Cream, 0.025%; ointment, 0.025%;
Kenalog	Triamcinolone acetonide	Spray, 0.2%; lotion, 0.025%; 0.1%; cream, 0.025%; 0.01%; ointment, 0.025%; 0.1%
Locorten	Flumethasone pivalate	Cream, 0.03%;
Oxylone	Fluorometholone	Cream, 0.025%;
Synalar	Fluocinolone acetonide	Solution, 0.01%; cream, 0.01%; 0.025%; ointment, 0.025%
Topicort L.P.	Desoximetasone	Cream, 0.05%
Tridesilon	Desonide	Solution, 0.05%; cream, 0.05%; ointment 0.05%
Uticort	Betamethasone benzoate	Gel, 0.025%; lotion, 0.025%; cream, 0.025%; ointment, 0.025%;
Valisone	Betamethasone valerate	Aerosol, 0.15%; lotion, 0.1%; cream, 0.1%; ointment, 0.025%;
Westcort	Hydrocortisone valerate	Cream, 0.2%

[a]Currently available in the United States.
[b]Estimated cost to the patient: 15–25¢ per gram.

Table 4-5 / High-Potency Topical Glucocorticosteroids[a,b]

Trade Name	Generic Name	Dosage Forms and Concentration
Aristocort	Triamcinolone acetonide	Cream, 0.5%; ointment, 0.5%;
Cyclocort	Amcinonide	Cream, 0.1%
Diprosone	Betamethasone dipropionate	Aerosol, 0.1%; lotion, 0.05%; cream, 0.05%;
Diprolene	Betamethasone dipropionate	Ointment 0.05%
Florone	Diflorasone diacetate	Cream, 0.05%; ointment, 0.05%
Halciderm	Halcinonide	Cream, 0.1%
Halog	Halcinonide	Solution, 0.1%; cream, 0.1%; ointment, 0.1%
Kenalog	Triamcinolone acetonide	Cream, 0.5%, ointment, 0.5%
Lidex	Fluocinonide	Cream, 0.05%, ointment, 0.05%;
Lidex-E	Fluocinonide	Cream, 0.05%;
Maxiflor	Diflorasone Diacetate	Cream, 0.05%; ointment, 0.05%
Synalar-HP	Fluocinolone acetonide	Cream, 0.2%
Topicort	Desoximetasone	Cream, 0.25%
Topsyn	Fluocinonide	Gel, 0.05%

[a]Currently available in the United States.
[b]Estimated cost to the patient: 15–30¢ per gram.

some consideration be given to a number of factors regarding therapy. General principles of topical therapy are listed in Table 4-6.

As a rule, it is appropriate to initiate topical therapy of an inflammatory dermatosis with a corticosteroid of higher potency and then to substitute an agent of lower potency once a positive response is observed. This approach is analogous to the slow tapering of systemically administered corticosteroids to reduce the risk of a rebound flare of the underlying disease.

Occlusion of the skin with an impermeable material such as a plastic film or suit is an effective method of enhancing the percutaneous absorption of topically applied corticosteroids at least 5–10-fold (63). This technique, while undoubtedly effective, has a number of drawbacks including patient discomfort due to heat and humidity, miliaria, and inhibition of the pituitary–adrenal axis, as well as greater side effects, such as atrophy.

Table 4-6 / General Principles of Topical Therapy with Glucocorticosteroids

Vehicle selection
Gels, solutions, lotions (acute dermatitis, hairy areas)
Creams, ointments (subacute and chronic dermatitis, glabrous skin)
Drug selection
Use more potent agents and taper to less potent agents
Amount prescribed
1–3 g per 9% body surface
20–30 g to cover the entire body in a single application

INTRALESIONAL Many dermatoses are characterized pathologically by inflammatory changes that occur in the mid to low dermis. Such anatomic localization tends to reduce the effectiveness of topically applied compounds. Furthermore, there are certain dermatologic diseases in which epidermal atrophy accompanies the primary disorder and makes topical therapy less desirable. Some diseases for which intralesional corticosteroid therapy is used are listed in Table 4-7. The various agents currently available for intralesional injection are listed in Table 4-8 (65). With the exception of the hexacetonide salt of triamcinolone, which has an inordinately long half-life, all these agents can be used in intralesional therapy. The usual dose varies from 1 to 10 mg/cc; all the preparations listed in Table 4-7 can be diluted with several solutions, including sterile water for injection (USP), sterile sodium chloride for injection (USP), sterile dextrose and sodium chloride for injection, and Xylocaine (lidocaine). In general, diluents containing parabens as preservatives should be avoided, as they may cause flocculation of the steroid. Selection of a drug for use may be guided by the desired duration of effect. The pharmacologically

Table 4-7 / Dermatologic Disorders Responsive to Intralesional Glucocorticosteroids

Inflammatory	*Infiltrative*	*Noninfectious granulomas*
Acne vulgaris	Keloids/hypertrophic scars	Granuloma annulare
Alopecia areata	Pretibial myxedema	Necrobiosis lipoidica diabeticorum
Eczema, localized		Sarcoidosis
Lichen planus		
Lupus erythematosus, discoid		
Lymphocytic infiltrate of Jessner/Kanof		
Lymphocytoma cutis		
Psoriasis		
Pyoderma gangrenosum		

active steroid moiety must first be cleaved enzymatically from the conjugated salt. In general, catalysis of the acetonide group occurs more slowly than does that of the diacetate or phosphate. Thus triamcinolone acetonide has a longer duration of action than exhibited by the other compounds.

The drugs can be introduced into the skin using a small-gauge (#25–#30) needle or using various devices that force the agent through the epidermis under pressure (Dermo-Jet or Mada-Jet). Caution should be exercised in the use of intralesional corticosteroids so that they are not injected intravascularly.

INTRAMUSCULAR Intramuscular administration of glucocorticosteroids is used extensively in the management of both acute and chronic dermatologic dis-

Table 4-8 / Glucocorticosteroids for Intralesional and Intramuscular Injection

Trade	*Generic Name*	*Dosage Forms and Concentrations*
Aristocort forte	Triamcinolone diacetate	Suspension, 40 mg/cc
Aristocort intralesional	Triamcinolone diacetate	Suspension, 25 mg/cc
Aristospan	Triamcinolone hexacetonide	Suspension 5 mg/cc
Celestone phosphate	Betamethasone sodium phosphate	Solution 4 mg/cc
Celestone soluspan	Betamethasone sodium phosphate and acetate	Solution of equal parts (3 mg/cc) of each salt
Decadron phosphate	Dexamethasone, sodium phosphate	Solution 4 and 24 mg/cc
Hexadrol phosphate	Dexamethasone, sodium phosphate	Solution 4 and 10 mg/cc
Kenalog-10	Triamcinolone acetonide	Suspension 10mg/cc
Kenalog-40	Triamcinolone acetonide	Suspension 40 mg/cc
Meticortelone acetate	Prednisolone acetate	Suspension 25 mg/cc

orders. In fact, some workers have suggested that this technique has advantages over orally administered corticosteroids (66), which are said to include the use of lower total doses and increased physician control of medication. However, this claim has engendered considerable controversy (67,68). The agents available for intramuscular injection are similar to those used for intralesional injection (see Table 4-8).

The major source of controversy in the use of intramuscular corticosteroids centers around their appropriateness in managing chronic dermatoses. All would agree that any corticosteroid administered in supraphysiologic doses chronically by whatever route will have considerable biochemical and clinical side effects and complications. Intramuscular injection of corticosteroids should be limited to the gluteus maximus muscle, and needles of sufficient length to penetrate the overlying subcutaneous fat should be used to minimize the risk of atrophy. Selection of an agent from Table 4-8 should be guided by the length of time in which antiinflammatory or immunosuppressive effects are desired by the therapist. In general, triamcinolone acetonide is metabolized more slowly than are the other drugs, and a pharmacologic effect can be expected to persist for 3–4 weeks. The other agents are effective for 7–10 days because they are more rapidly metabolized (69,70).

SYSTEMIC The clinical use of systemic corticosteroids in dermatologic practice is essential for the management of a variety of disorders, both acute and chronic (Table 4-9). Because of the profound inhibitory effects exerted by these agents on immunologic and inflammatory responses, they are highly efficacious in the treatment of numerous diseases that have cutaneous manifestations. The use of systemic corticosteroids is not limited by their lack of therapeutic efficacy, but rather by the myriad of toxic effects associated with their use.

A representative list of selected acute and chronic disorders in which systemic corticosteroids are effective and useful may be found in Table 4-9.

Orally administered corticosteroids are generally used in three major ways: single daily dose, divided daily dose, and alternate-day dose.

Many of the suppressive effects of corticosteroids on immunologic and inflammatory responses are short-lived and can be directly correlated with the dose of drug (amount and interval) and its plasma half-life (Table 4-10). Ideal management of a pathologic process secondary to inflammatory or immunologic aberrations would consist of regularly administered doses of drug sufficiently high to inhibit the reaction completely. Unfortunately, such an approach is for the most part unacceptable because of the toxicity of these agents.

Single daily dose: The single daily dose of corticosteroids has a number of advantages (71,72). First, it is easier for the patient to remember

Table 4-9 / Dermatologic Disorders in which Systemic Corticosteroids are Effective and Useful

Acute	*Chronic*
Allergic contact dermatitis	Eczematous dermatitis
Atopic dermatitis	Atopic
Lichen planus	Dyshidrotic
Exfoliative erythroderma	
Generalized pustular psoriasis	
Herpes zoster (patients greater than 60 years of age)	

Table 4-10 / Comparative Pharmacologic Activity of Commonly Used Systemic Corticosteroids[a]

Drug	*Dose equivalent (mg)*	*Plasma half-life (min)*
Cortisone	25	30
Hydrocortisone	20	90
Prednisone	5	60
Prednisolone	5	200
Methylprednisolone	4	180
Triamcinolone	4	200
Dexamethasone	0.75	200

[a]Modified from Merkle AW, Tyler FH: Potency and duration of action of glucocorticoids. Am J Med 63: 200–207, 1977.

to take the drug. Second, when given in the morning after breakfast, it has substantially fewer inhibitory effects on the hypothalamic–pituitary–adrenal axis than occur with equivalent doses administered in divided amounts (73). A single morning dose of 10 mg of prednisone produces a negligible adrenal suppression, as compared with 2.5 mg given 4 times a day (72). The adrenal cortex produces endogenous cortisol on a daily basis in accordance with a circadian rhythm that is dependent on the hypothalamus, which elaborates corticotropin release factors that stimulate the pituitary to secrete adreno-corticotropic hormone (ACTH), which in turn enhances cortisol production by the zona fasciculata of the adrenal cortex. Cortisol secretion is regulated by a negative feedback mechanism whereby elevated plasma cortisol shuts off the hypothalamic corticotropin release factors, decreasing secretion of ACTH. The reverse occurs when cortisol diminishes. This system is organized such that maximum plasma cortisol levels occur at 8 o'clock AM and fall to minimum levels approximately 12 hours later.

Since the maximum endogenous inhibitory effect on the axis occurs at 8 o'clock AM, it is generally believed that the timing of exogenous doses of corticosteroid to coincide with this phase of the circadian rhythm will minimize the suppressive effects of the drugs on the adrenal cortex (74).

Divided daily dose: Since an active ongoing inflammatory and immunologic process must be suppressed by continuous inhibitory levels of drug, it is frequently necessary to administer corticosteroids in divided daily doses. Once the condition is adequately controlled, it is then possible to switch the patient to the other regimens, which may have less antiinflammatory and immunosuppressive effects. Some believe that the inhibitory effects of the divided-dose regimen on dermatologic disorders are not sufficiently superior to the single-dose regimen to warrant the use of the former except in rare circumstances (74).

Alternate-day dose: This approach was first advocated in 1961 and has been widely used in an effort to reduce the considerable toxicity of systemically administered corticosteroids (75). Subsequently it was shown that the various pharmacologic properties of corticosteroids, such as antiinflammatory effect, ACTH-suppressing effect, and plasma half-life, are independent variables (76). This finding suggested that lengthening the intervals between administration might permit sufficient effectiveness to combat disease while simultaneously reducing the toxic effects of these agents (76).

It has been emphasized that it is rarely possible to obtain adequate control of a steroid-responsive disease by initiating therapy with an alternate-day regimen (77). However, it is quite feasible to maintain a state of suppression of inflammatory and immunologic responsiveness previously induced by daily regimens using the alternate-day approach.

Conversion to an alternate-day regimen must be carried out carefully, and there is no generally agreed-upon formula for achieving it successfully. One may gradually increase the dose on the second day (78). Changes in dose should be approximately 10 mg of prednisone (or equivalent) at total daily doses of 50 mg and above, 5 mg of total daily doses of 20–50 mg, and 2.5 mg at lower total daily doses. The interval between changes in dose will vary depending on the patient's clinical status.

Another approach is to simply double the daily dose and abruptly discontinue treatment on the alternate day. In our experience, this approach is more often accompanied by a flareup of the underlying disease.

An intermediate method is to raise and lower the dose on successive

days by equal amounts until the alternate-day regimen has been implemented. During the tapering of the "off" day, it may be helpful to use nonsteroidal antiinflammatory drugs to afford symptomatic relief of the disorder being treated.

The alternate-day method of administering corticosteroids is primarily useful in reducing the side effects and complications of these drugs. It is said that virtually all are reduced or abolished except for posterior subcapsular cataracts (79). However, in our experience cushingoid features can occur in patients receiving high doses of corticosteroids on alternate days for prolonged periods. These general guidelines should be kept in mind for alternate-day therapy:

1. Use intermediate-acting corticosteroids such as prednisone or prednisolone.
2. Switch to a single morning dose.
3. Switch to an alternate-day regimen as soon as practical.

Another modality that has been recently recommended is known as pulse therapy (80,81). Pulse therapy is the daily parenteral administration of supra-pharmacologic doses of methylprednisolone sodium succinate for short periods. For a typical regimen employed in treating patients with pyoderma gangrenosum, methylprednisolone sodium succinate for injection (1 g in 150 ml of 5 percent dextrose) is infused during a 60–90-minute period daily at 9 o'clock AM for 5 days. This has provided significant benefit to patients who otherwise failed to respond to orally administered drug in high doses.

Side Effects/Complications The glucocorticosteroids have proved a remarkably safe and effective therapeutic tool for the practicing dermatologist. Yet there is no question that the abuse of these drugs can lead to serious and occasionally life-theatening sequelae. The hazards of the glucocorticosteroids are discussed for each category of agent.

TOPICAL The newer fluorinated corticosteroids are highly potent agents that can penetrate human skin and produce systemic effects. Ample data show that topically applied corticosteroids, particularly under occlusive wraps, can cause disturbances in the hypothalamic–pituitary–adrenal axis (82–96). These side effects are simply the systemic sequelae of percutaneous absorption of topically applied drugs and have usually occurred in patients with widespread disease treated in a hospital setting (Fig. 4-7). Furthermore, rebound flareup of an underlying dermatosis can occur after abrupt cessation of topical corticosteroid therapy (97,98).

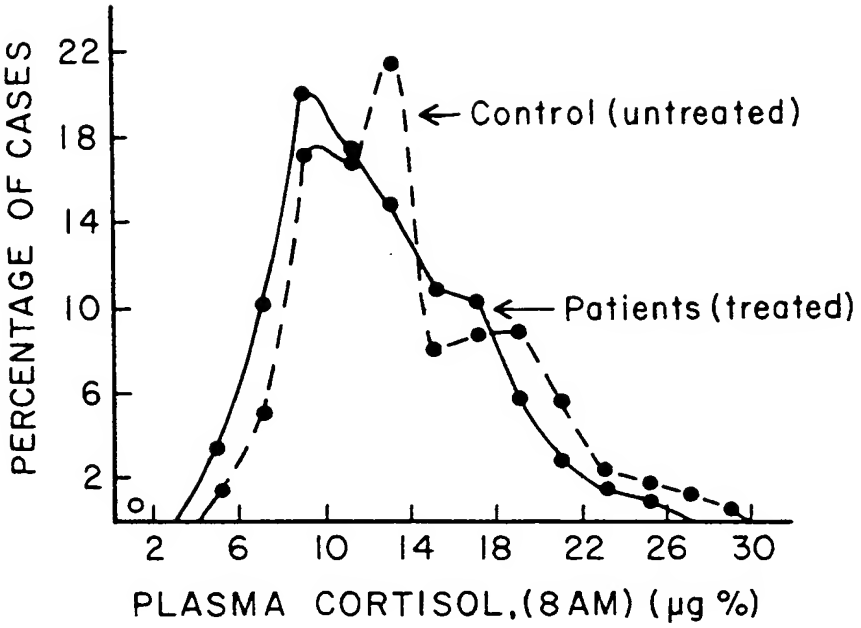

Figure 4-7 *Relative lack of effect of repeated application of topical corticosteroids on plasma cortisol levels in ambulatory patients.*

Three major methods are available for assessing the integrity of the pituitary–adrenal axis (99):

1. *Responsiveness of the adrenal gland to exogenous ACTH.* ACTH can be infused intravenously (5 U/h for 8 hours), or synthetic ACTH (CORTrosyn) can be injected intramuscularly (25 μg). Increases in plasma cortisol and in urinary excretion of 17-hydroxycorticosteroids indicate a responsive adrenal cortex.
2. *Metyrapone* Administration of this drug assesses pituitary reserve by stimulating ACTH secretion. This effect is achieved because the drug is a potent inhibitor of 11β-hydroxylase, the enzyme that catalyzes the final step in cortisol biosynthesis. Thus metyrapone reduces cortisol secretion, thereby eliciting an increase in pituitary ACTH to stimulate further cortisol production, which can be detected by measuring 17-hydroxycorticosteroids in urine. Metyrapone is administered orally in doses of 10 mg/kg body weight every 4 hours for 6 doses. A normal response is a 2-fold increase in total urinary 17-hydroxycorticosteroids on the day of treatment or the following day.
3. *Insulin-induced hypoglycemia* Infusion of insulin causes an

increase in pituitary ACTH production that increases plasma cortisol concentrations within approximately 1 hour (88).

As shown in Fig. 4-8, a considerable lag phase frequently occurs in the recovery of pituitary and adrenal responsiveness after prolonged therapy with glucocorticosteroids. The recovery process may require 9–12 months in patients who have been profoundly suppressed by exogenous drugs for 1 year or more. It should be reemphasized that this degree of suppression is unlikely to occur with topically applied drugs. However, children are more susceptible to the growth-inhibiting effects of topically applied corticosteroids and, because of their large body surface, are uniquely susceptible to percutaneous absorption of these agents (90).

Perhaps the most common dermatologic complication accompanying the use of the more potent fluorinated glucocorticosteroids is atrophy and stria formation. This complication is manifested by thinning of the epidermis and dermis, telangiectasia, increased vascular fragility leading to purpura, and stellate pseudoscars (100–102). These complications occur much more commonly in intertriginous areas or after chronic occlusive therapy and appear to be directly related to the potency of the drug used and to the chronicity of therapy.

Topical fluorinated corticosteroids are associated with acneiform and rosacea-like eruptions on the face with pustules, telangiectasias, and persistent erythema; these problems clear within several months of discontinuing the medication or when a nonfluorinated drug such as hydrocortisone (103) is substituted.

Furthermore, the fluorinated derivatives have been incriminated in causing a perioral eruption consisting of symmetrical follicular papules and pustules around the mouth leaving an uninvolved zone immediately adjacent to the lips (104). The perioral dermatitis may subside after substitution of a nonfluorinated glucocorticosteroid and the administration of oral tetracycline in daily doses ranging from 500 to 1000 mg (105).

Other less common side effects include allergic contact dermatitis (106), hypopigmentation (107), facial hypertrichosis (108), the masking of dermatophyte infections, so-called tinea incognito (109), and exacerbation of scabies and candidiasis (110, 111). Other side effects include induction of acne and wasting of the diaper area in infants (112,113). Glycosuria and hyperglycemia may also occur in selected patients (114).

INTRALESIONAL These agents have side effects similar to those of the potent topical agents described earlier. Specifically, atrophy, changes in pigmentation, and telangiectasia can all occur (115,116). As pointed out by Callen

(65), intralesional corticosteroids should not be used in anatomic areas in which the skin is thin. Lower doses should be used on the face, lips, and buccal mucosa, which are particularly susceptible to atrophy. Pituitary–adrenal suppression appears to be a minimal risk in patients treated with intermittent intralesional corticosteroids (117). Occasionally intralesional injection may result in cellulitis, which may require treatment with appropriate antibiotics. Intralesional corticosteroids when used properly offer an effective supplement to topical compounds and may reduce the need for systemic therapy in many patients.

INTRAMUSCULAR Considerable controversy surrounds the use of intermittent intramuscular injections of corticosteroids for the management of chronic dermatologic diseases (66–70), whereas the use of these agents for acute self-limited processes is more generally accepted. The controversy centers about the purported advantages of repeated intramuscular injection versus chronic oral administration of corticosteroids, particularly insofar as relative safety is concerned. One observer strongly believes that intramuscular triamcinolone acetonide has significant toxicity and is much more likely to cause hypothalamic–pituitary–adrenal suppression than is orally administered drug. Several studies have clearly shown that as many as half the patients receiving intermittent intramuscular corticosteroids will have decreased AM plasma cortisol for as long as 4–6 weeks after the previous injection (69,118,119).

Other observers who espouse the use of intramuscular corticosteroids cite as advantages the slow release and physician control of the medication as well as equivalent hypothalamic–pituitary–adrenal suppression of the two modalities (120). It is generally agreed that intermittent intramuscular administration of corticosteroids does have a greater tendency to aggravate solar purpura of the arms and shins and to induce hypermenorrhea in 25–30 percent of women so treated.

One study has compared the side effects of orally administered prednisone and intramuscular triamcinolone acetonide in patients with asthma (121). The results are summarized in Table 4-11.

SYSTEMIC The untoward effects of systemically administered corticosteroids on a chronic basis frequently present the therapist with difficult decisions in the management of patients with dermatologic disorders. The list of complications attributed to the use of these drugs is indeed a long and intimidating one (Table 4-12) and, were it not for their unquestioned efficacy, their suitability for therapy of skin disease would be highly questionable. This raises the question that must always be considered, namely the risk–benefit ratio of a modality. In general risk–benefit ratios are an important variable that must enter into the therapeutic decision-making process. Risk can be de-

Table 4-11 / Comparative Side Effects of Orally Administered Prednisone and Intramuscularly Administered Triamcinolone[a]

Side Effect	Drug	
	Prednisone	*Triamcinolone*
Cushingoid features	20	1
Purpura	5	10
Hypertension	1	4
Fat necrosis	0	1
Osteoporosis	3	1
Hyperglycemia	0	1
Cataract	1	1

[a]Modified from Peake, et al: Triamcinolone in corticosteroid :esistant asthma. *Br J Dis Chest* 73: 39–44, 1979.

Table 4-12 / Side Effects and Complications of Systemically Administered Glucocorticosteroids

Hematologic
- Neutrophilia
- Monocytopenia
- Lymphocytopenia
- Eosinopenia

Metabolic
- Obesity
- Growth disturbances
- Na+ and K+ loss
- Hyperglycemia
- Glycosuria
- Hypertension
- Osteoporosis

Dermatologic
- Atrophy
- Striae
- Bruisability/purpura
- Telangiectasia
- Acne/rosacea

Infectious
- Increased susceptibility to bacterial, mycobacterial and deep fungal infection

Ophthalmologic
- Cataracts posterior sub-capsular; glaucoma

fined as the product of two factors: the probability of its occurrence and the degree of harm. Toxicity that has a high probability of occurrence can only be acceptable if the degree of harm is relatively low. Conversely, if the degree of harm is very high, the probability of occurrence must be quite low to be acceptable (122). Systemic corticosteroids have multiple toxic effects, but their predictability in an individual patient is difficult to define. Many of the toxic effects have a relatively moderate degree of harm and are thus acceptable in managing more severe dermatologic disorders. Clearly life-threatening diseases such as pemphigus and pemphigoid demand the use of high-dose systemic corticosteroids, since the degree of harm associated without such treat-

ment clearly outweighs the degree of harm that accompanies administration of the drugs. On the other hand, chronic disorders such as atopic dermatitis are frequently quite debilitating but are rarely fatal. This makes the decision to use systemic corticosteroids more difficult and is an example of the importance of the art as compared with the science of medicine.

There are at least three major types of adverse effects of the therapeutic use of systemic corticosteroids (123):

1. Adrenal insufficiency after withdrawal of therapy as a consequence of continued inhibition of hypothalamic ACTH-releasing factor and/or adrenal atrophy secondary to previous corticosteroid therapy (Fig. 4-8)
2. Iatrogenic hyperadrenocorticism leading to clinicopathologic manifestations resembling Cushing's disease
3. Rebound flareup of the disease process subdued during therapy

In addition to these major and inevitable complications of systemic corticosteroid therapy, other complications occur in some patients as well (124). These are discussed briefly according to the organ system affected.

DERMATOLOGIC The cutaneous manifestations of corticosteroid toxicity include atrophy, striae, acne/folliculitis/rosacea, purpura, and stellate pseudo-

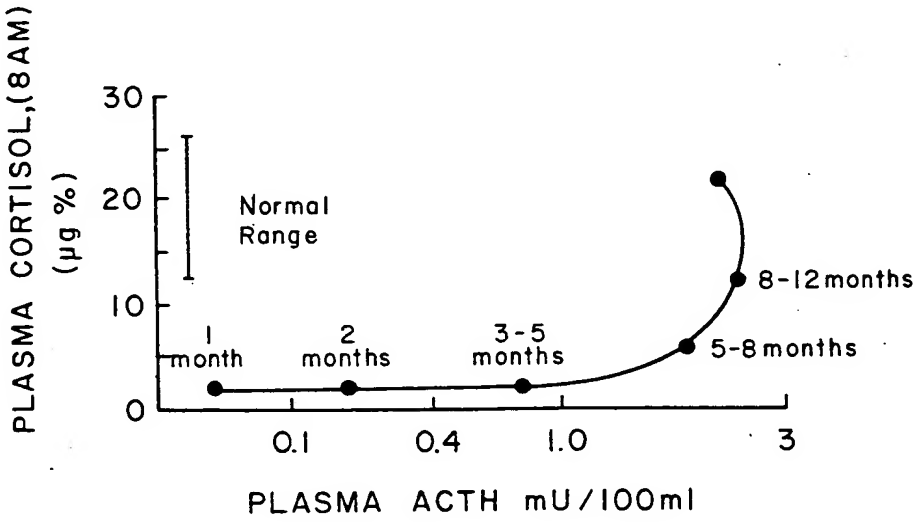

Figure 4-8 *Recovery from pituitary–adrenal suppression induced by systemically administered corticosteroids requires 9–12 months.*

scarring. In general, these can occur with either topical or systemic therapy. The atrophy, striae, and pseudoscarring are generally not reversible, whereas the acne/folliculitis/rosacea and purpura generally remit after cessation of therapy (125).

HEMATOLOGIC The changes in the circulating blood include lymphocytopenia, eosinopenia, monocytopenia, and a neutrophilic granulocytosis (126). These side effects are all reversible upon discontinuing the medication.

MUSCULOSKELETAL Osteoporosis is a major complication of corticosteroid therapy and generally occurs after prolonged treatment (127). The mechanism of this effect may relate to abnormalities in vitamin D metabolism, which in turn diminishes gastrointestinal absorption of calcium (128,129). It is entirely possible that certain subsets of the population are at particular risk for this complication (130). Thus the elderly, postmenopausal women, and persons with inadequate dietary calcium may be uniquely susceptible to corticosteroid-induced osteoporosis. Recent studies indicate that ascorbic acid deficiency may contribute to osteoporosis and that repletion of ascorbate in patients treated with corticosteroids may reduce the risk of various catabolic effects of these agents on collagen synthesis (131).

Aseptic necrosis of the femoral head is thought to occur more frequently in patients treated with corticosteroids (132). This may relate to the general tendency of these drugs to produce fatty emboli, which can lodge in various compartments. Myopathy also occurs in association with muscle wasting as another catabolic effect of these drugs (133).

Additional effects of these drugs include growth retardation (particularly in pediatric patients), hyperglycemia secondary to enhanced hepatic gluconeogenesis and to antagonism of peripheral insulin effects, altered fat distribution (cushingoid appearance), hypertriglyceridemia, pancreatitis, sodium retention, potassium wasting, posterior subscapsular cataracts, glaucoma (open-angle), psychosis, and pseudotumorce rebri (74).

Systemic corticosteroids also have profound effects on immunologic and inflammatory responses and are therefore associated with an increased risk of infections including those caused by bacteria, viruses, fungi, and parasites (134). Ironically, systemically administered corticosteroids are also quite useful in the management of the severe morbidity that accompanies certain infections such as typhoid fever, brucellosis, and miliary tuberculosis. It has also been shown that a 3-week course of these drugs may substantially reduce the risk of post-herpetic neuralgia in older individual with herpes zoster (135, 136).

REFERENCES

1. GUBNER R: Therapeutic suppression of tissue reactivity. I. Comparison of the effects of cortisone and aminopterin. *Am J Med Sci 221*: 169–175, 1951.
2. GUBNER R, COTE L, HUGHES J, et al: Comparative effects of aminopterin, cortisone and ACTH in experimental formaldehyde arthritis and psoriatic arthritis. *J Invest Dermatol 19*: 297–305, 1952.
3. GOLDMAN L, THOMPSON RG, TRICE ER: Cortisone acetate in skin disease. Local effect in the skin from topical application and local injection. *Arch Dermatol 65*: 177–186, 1952.
4. SULZBERGER MB, WITTEN VH: The effect of topically applied compound F in selected dermatoses. *J Invest Dermatol 19*: 101–102, 1952.
5. FITZPATRICK TB, GRISWOLD N-C, HICKS JH: Sodium retention and edema from percutaneous absorption of fluorocortisone acetate. JAMA *158*: 1149, 1955.
6. LANDAU BR, MAHLER R, ASHMORE J, et al: Cortisone and the regulation of hepatic gluconeogenesis. *Endrocrinology 70*: 47–53, 1962.
7. GOLDSTEIN L, STELLA EJ, KNOX WE: The effect of hydrocortisone on tyrosine-ketoglutarate transaminase and tryptophan pyrrolase activities in the isolated, perfused rat liver. *J Biol Chem 237*: 1723–1726, 1962.
8. DLUHY RG, LAULER DP, THORN GW: Pharmacology and chemistry of adrenal glucocorticosteroids. *Med Clin North Am 57*: 1155–1165, 1973.
9. MCKENZIE AW, ATKINSON RM: Topical activities of betamethasone esters in man. *Arch Dermatol 89*: 741–746, 1964.
10. WEISSMAN NG, THOMAS L: The effects of corticosteroids upon connective tissue and lysosomes. *Recent Prog Horm Res 20*: 215–245, 1964.
11. WEISSMAN NG, FELL HB: The effect of hydrocortisone on the response of fetal rat skin in culture to ultraviolet irradiation. *J Exp Med 116*: 365–380, 1962.
12. WEISSMAN NG: Studies of lysosomes. VI. The effect of neutral steroids and bile acids on lysosomes *in vitro*. *Biochem Pharmacol 14*: 525–535, 1965.
13. ALLISON AC: Effects of glucocorticosteroids on lymphocytes and macrophages. *Clin Exp Dermatol 4*: 135–138, 1979.
14. DOUGHERTY TF: Effects of corticosteroid hormones on lymphatic tissues, in *The Lymphocytes and Lymphocytic Tissue*, Rebuck JW (ed), pp 112–124. New York: Hoeber, 1960.
15. BALOW JE, HURLY DL, FAUCI AS: Immunosuppressive effects of glucocorticosteroids. Effects of acute vs chronic administration on cell mediated immunology. *J Immunol 114*: 1072–1076, 1975.
16. WAHL SM, ALTMAN LC, ROSENSTREICH DC: Inhibition of *in vitro* lymphokine synthesis by glucocorticosteroids. *J Immunol 115*: 476–484, 1975.
17. FAUCI AS, DALE DC: The effects of hydrocortisone on the kinetics of normal hyman lymphocytes. *Blood 46*: 235–243, 1975.
18. MCMILLAN R, LONGMIRE R, YELEROSKY T: Effect of corticosteroids on human IgG synthesis. *J Immunol 116*: 1592–1602, 1976.
19. SAXON A, STEVENS RH, RAMER SJ, et al: Glucocorticosteroids administered *in vivo* inhibit human suppressor T lymphocyte function and diminish B lymphocyte responsiveness in *in vitro* IgG synthesis. *J Clin Invest 61*: 922–1000, 1978.

20. SCHREIBER AD, PARSONS J, MCDERMOTT P: Effect of corticosteroids on the human monocyte IgG and C receptors. *J Clin Invest* 56: 1187–1189, 1975.
21. THOMPSON J, VAN FURTH R: The effect of glucocorticoids on the kinetics of monocytes and peritoneal macrophages, in *Mononuclear Phagocytes*, van Furth R (ed), pp 255–281. Oxford: Blackwell Scientific Publications, 1970.
22. ALLISON AC, FERLUGA J, PRYDZ H, et al: The role of macrophage inflammation in chronic inflammation. *Agent Actions 8*: 27–35, 1978.
23. GLOTT M, KALIN H, WAGNER K, et al: Prostaglandin release from macrophages: an assay system for anti-inflammatory drugs *in vitro*. *Agents Actions 7*: 321–326, 1977.
24. FAUCI AS, DALE DC, BALOW JE: Glucocorticosteroid therapy: Mechanisms of action and clinical considerations. *Ann Intern Med 84*: 304–315, 1976.
25. DALE DC, FAUCI AS, GUERRY D, et al: Comparison of agents producing a neutrophilic leukocytosis in man: Hydrocortisone, prednisone, endotoxin, and etiocholanolone. *J Clin Invest 56*: 808–813, 1975.
26. BISHOP CR, ATHENS JW, BOGGS DR, et al: Leukokinetic studies XIII. A new steady-state kinetic evaluation of the mechanism of cortisone-induced granulocytosis. *J Clin Invest 53*: 240–246, 1974.
27. ATHENS JW, HAAB OP, RAAB SO, et al: Leukokinetic studies. IV. The total blood circulating and marginal granulocyte pools and the granulocyte turnover rate in normal subjects. *J Clin Invest 40*: 989–995, 1961.
28. BOGGS DR, ATHENS JW, CARTWRIGHT GE, et al: The effect of adrenal glucocorticosteroids upon the cellular composition of inflammatory exudates. *Am J Pathol 44*: 763–773, 1964.
29. CLARK RAF, GALLIN JI, FAUCI AS: Effects of *in vivo* prednisone on *in vitro* eosinophil and neutrophil adherence and chemotaxis. *Blood 53*: 633–641, 1979.
30. MAJESKI JA, ALEXANDER JW: The steroid effect on the *in vitro* human neutrophil chemotactic response. *J Surg Res 21*: 265–272, 1976.
31. RINEHART JJ, SARGONE AL, BABCERZAK SP, et al: Effects of corticosteroid therapy on human monocyte function. *N Engl J Med 292*: 236–241, 1975.
32. CLAMAN HN: Corticosteroids and lymphoid cells. *N Engl J Med 287*: 388–397, 1972.
33. COHEN JJ: Thymus derived lymphocytes sequestered in the bone marrow of hydrocortisone-treated mice. *J Immunol 108*: 841–844, 1972.
34. FAUCI AS: Mechanism of corticosteroid action on lymphocyte subpopulations. I. Redistribution of circulating T and B lymphocytes to the bone marrow. *Immunology 28*: 669–680, 1975.
35. FORD WL, GOWANS JL: The traffic of lymphocytes. *Semin Hematol* 6: 67–83, 1969.
36. FAUCI AS, DALE DC: Alternate-day prednisone therapy and human lymphocyte subpopulations. *J Clin Invest 55*: 22–32, 1975.
37. RINEHART JJ, SAGONE AL, BALCERZAK SP, et al: Effects of corticosteroid on monocyte function. *J Clin Invest 54*: 1332–1343, 1974.
38. WESTON WL, MANDEL MJ, YECKLEY JA, et al: Mechanism of cortisol inhibition of adoptive transfer of tuberculin sensitivity. *J Lab Clin Med 82*: 366–371, 1973.
39. CRADDOCK CG, WINKELSTEIN A, MATSUYUKI Y, et al: The immune response to

foreign red blood cells and the participation of short-lived lymphocytes. *J Exp Med 125*: 1149–1172, 1967.
40. ZURIER RB, WEISSMAN G: Anti-immunologic and anti-inflammatory effects of steroid therapy. *Med Clin North Am 57*: 1295–1307, 1973.
41. COWLING DC, QUAGLINO D: Effects of some antigens on leukocyte cultures. *J Pathol 89*: 63–71, 1965.
42. NORRIS DA, CAPIN L, WESTON WL: The effect of epicutaneous glucocorticosteroids on human monocyte and neutrophil migration *in vivo*. *J Invest Dermatol 78*: 386–390, 1982.
43. FISHER LB, MAIBACH HI: The effects of corticosteroids on human epidermal mitotic activity. *Arch Dermatol 103*: 39–44, 1971.
44. BAXTER DL, STOUGHTON RB: Mitotic index of psoriatic lesions treated with anthralin, glucocorticosteroid, and occlusion only. *J Invest Dermatol 54*: 410–412, 1970.
45. DUVIVIER A, STOUGHTON RB: Tachyphylaxis to the action of topically applied glucocorticosteroids. *Arch Dermatol 111*: 581–583, 1975.
46. DUVIVIER A, PHILLIPS H, HEHIR M: Applications of glucocorticosteroids. The effects of twice daily vs once-every-other-day applications on mouse epidermal cell DNA synthesis. *Arch Dermatol 118*: 305–308, 1982.
47. MCKENZIE AW, ATKINSON RM: Topical activities of betamethasone esters in man. *Arch Dermatol* 89: 741–746, 1964.
48. STOUGHTON RB: Vasoconstrictor activity and percutaneous absorption of glucocorticosteroids—a direct comparison. *Arch Dermatol 99*: 753–756, 1969.
49. REID J, BROOKS DB: Topical corticosteroids—an experimental evaluation of the vasoconstrictor test as an index of anti-inflammatory activity. *Br J Dermatol 80*: 328–336, 1968.
50. STOUGHTON RB: Bioassay system for formulations of topically applied glucocorticosteroids. *Arch Dermatol 106*: 825–827, 1972.
51. VICKERS CHF: Existence of reservoir in the stratum corneum. *Arch Dermatol 88*: 20–23, 1963.
52. UITTO J, TEIR H, MUSTAKALLIO K: Corticosteroid-induced inhibition of the biosynthesis of human skin collagen. *Biochem Pharmacol 21*: 2161–2167, 1972.
53. MEIKLE AW, TYLER FH: Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. *Am J Med 63*: 200–207, 1977.
54. MEIKLE AW, CLARKE DH, TYLER FH: Cushing's syndrome resulting from a low dose of dexamethasone. A result of slow plasma clearance. *JAMA 235*: 1592–1593, 1976.
55. KOWOZER M, VEATCH L, KAPLAN MM: Decreased clearance of prednisolone, a factor in the development of corticosteroid side effects. *J Clin Endocrinol Metab 38*: 407–412, 1974.
56. BROOKS SM, WERK EE, ACKERMAN SJ, et al: Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N Engl J Med 286*: 1125–1128, 1972.
57. CHROUSOS GP, VINGERHOLDS A, BRANDON D, et al: Primary cortisol resistance in man. A glucocorticoid receptor-mediated disease. *J Clin Invest 69*: 1261–1269, 1982.

58. KATZ M, POULSON BJ: Corticoid, vehicle and skin interaction in percutaneous absorption. *J Soc Cosmet Chem 23*: 565–590, 1972.
59. BURDICK KH, HALEBLIAN JK, POULSEN BJ, et al: Corticosteroid ointments: Comparison by two human bioassays. *Curr Ther Res 15*: 233–242, 1973.
60. POULSEN BJ, YOUNG E, CEQUILLA V, et al: Effect of topical vehicle composition on the *in vitro* release of fluocinolone acetonide and its acetate ester. *J Pharm Sci 57*: 928–933, 1968.
61. ROBERTSON DB, MAIBACH HI: Topical corticosteroids. *Int J Dermatol 81*: 59–67, 1982.
62. MALKINSON FD, FERGUSON EH: Percutaneous absorption of hydrocortisone-1-C^{14} in two human subjects. *J Invest Dermatol 25*: 281–283, 1955.
63. FELDMANN RF, MAIBACH HI: Penetration of ^{14}C-hydrocortisone through normal skin: the effect of stripping and occlusion. *Arch Dermatol 91*: 661–666, 1965.
64. LEE SS: Topical steroids. *Int J Dermatol 20*: 632–641, 1981.
65. CALLEN JP: Intralesional corticosteroids. *J Am Acad Dermatol 4*: 149–151, 1981.
66. ARNOLD HL JR.: Systemic steroid therapy with intramuscularly injected tramcinolone. *South Med J 71*: 102–107, 1978.
67. STORRS FJ: Intramuscular corticosteroids: A second point of view. *J Am Acad Dermatol 5*: 600–602, 1981.
68. REES RB: Oral vs parenteral corticosteroids: A clinical controversy. *J Am Acad Dermatol 5*: 602–604, 1981.
69. MIKHAIL GR, LIVINGOOD CS, MELLINGER RC, et al: Effect of long-acting parenteral corticosteroids on adrenal function. *Arch Dermatol 100*: 263–268, 1969.
70. MIKHAIL GR: Intramuscular corticosteroids. *J Am Acad Dermatol 5*: 605–606, 1981.
71. THORN GW: Clinical considerations in the use of corticosteroids. *N Engl J Med 274*: 775–781, 1966.
72. FINE RM: Physiologic effects of systemic corticosteroids in dermatology. *Cutis 11*: 217–226, 1973.
73. GRANT SD, FORSHAM PH, DIRAIMONDO VC: Suppression of 17-hydroxycorticosteroids in plasma and urine by single and divided doses of triamcinolone. *N Engl J Med 273*: 1115–1118, 1965.
74. STORRS FJ: Use and abuse of systemic corticosteroid therapy. *J Am Acad Dermatol 1*: 95–105, 1979.
75. REICHLING GH, KLIGMAN AM: Alternate-day corticosteroid therapy. *Arch Dermatol 83*: 980–983, 1961.
76. HARTER JG, REDDY WJ, THORN GW: Studies on an intermittent corticosteroid dosage regimen. *N Engl J Med 269*: 591–596, 1963.
77. FAUCI AS: Alternate-day corticosteroid therapy. *Am J Med 64*: 729–731, 1978.
78. AXELROD L: Glucocorticoid therapy. *Medicine 55*: 39–65, 1976.
79. WINTER RJ, KERN F, BLIZZARD RM: Prednisone therapy for alopecia areata: a follow-up report. *Arch Dermatol 112*: 1549–1552, 1976.
80. JOHNSON RB, LAZARUS GS: Pulse therapy: Therapeutic efficacy in the treatment of pyoderma gangrenosum. *Arch Dermatol 118*: 76–84, 1982.
81. WILLIAMS IA, BAYLIS EM, SHIPLEY ME: A double-blind placebo-controlled trial of methylprednisolone pulse therapy in active rheumatoid disease. *Lancet 2*: 237–240, 1982.

82. GELL KA, BAXTER DL: Plasma cortisol suppression by steroid creams. *Arch Dermatol 89*: 734–740, 1964.
83. MARCH C, KERBEL G: Adrenal function after topical application of topical steroids under occlusive plastic film. *JAMA 187*: 676–678, 1964.
84. KIRKETEPP M: Systemic effects of local treatment with fluocinolone acetonide applied under plastic film. *Acta Derm Venereol (Stockh) 44*: 54–62, 1964.
85. MARCH C, REA TH JR, PORTER MJ: Adrenal function after topical steroid therapy. *Clin Pharmacol Ther* 6: 43–49, 1965.
86. SCOGGINS RB, KLIMAN B: Percutaneous absorption of corticosteroids. Systemic effects. *N Engl J Med 273*: 831–840, 1965.
87. TAYLOR KS, MALKINSON FD, GAK C: Pituitary adrenal function following topical triamcinolone acetonide and occlusion. *Arch Dermatol 92*: 174–177, 1982.
88. JAMES VHT, MUNRO DD, FEIWEL M: Pituitary-adrenal function after occlusive topical therapy with betamethasone -17-valerate. *Lancet 2*: 1059–1061, 1967.
89. CARR RD, TARNOWSKI WM: Percutaneous absorption of corticosteroids. Adrenocortical suppression with total body inunction. *Acta Derm Venereol (Stockh) 48*: 417–428, 1968.
90. FEIWEL M, JAMES VHT, BARNETT ES: Effect of potent topical steroids on plasma-cortisol levels of infants and children with eczema. *Lancet 1*: 485–487, 1969.
91. SCOTT M, MALMSTEN LA, THELIN I: Effect on plasma cortisol level and urinary cortisol excretion in healthy volunteers, after application of three different steroid ointments under occlusion. *Acta Derm Venereol 61*: 543–546, 1981.
92. WILSON L, WILLIAMS DI, MARSH SD: Plasma corticosteroid levels in out-patients treated with topical steroids. *Br J Dermatol 88*: 373–380, 1973.
93. MUNRO DD, CLIFT DC: Pituitary-adrenal function after prolonged use of topical corticosteroids. *Br J Dematol 88*: 381–385, 1973.
94. BROMLEY PA, MULLER FO, MALAN J, et al: Plasma cortisol levels in normal volunteers receiving either betamethasone valerate or desoximetasone by topical application. *South Afr Med J 54*: 239–241, 1978.
95. STAUGHTON RCD, AUGUST PJ: Cushing's syndrome and pituitary-adrenal suppression due to clobetasol propionate. *Br Med J II*: 419–421, 1975.
96. CARRUTHERS JA, AUGUST PJ, STAUGHTON RCD: Observations on the systemic effect of topical clobetasol propionate (Dermovate). *Br Med J IV*: 203–204, 1975.
97. BOXLEY JD, DAWBER RPR, SUMMERLY R: Generalized pustular psoriasis on withdrawal of clobetasol propionate ointment. *Br Med J II*: 255–256, 1975.
98. BAKER H, RYAN TJ: Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. *Br J Dermatol 80*: 771–784, 1968.
99. WILLIAMS RH: *Textbook of Endocrinology,* 6th ed, pp 264–265. Philadelphia: WB Saunders, 1981.
100. STEVANOVIC DV: Corticosteroid-involved atrophy of the skin with telangectasia. A clinical and experimental study. *Br J Dermatol 87*: 548–556, 1972.
101. COLOMB D: Stellate spontaneous pseudoscars. *Arch Dermatol 105*: 551–554, 1972.
102. EPSTEIN N, EPSTEIN WL, EPSTEIN JH: Atrophic striae in patients with inguinal intertrigo. *Arch Dermatol 87*: 450–455, 1963.

103. SNEDDON I: Adverse effect of topical fluorinated corticosteroids in rosacea. *Br Med J I*: 671–673, 1969.
104. SNEDDON I: Perioral dermatitis. *Br J Dermatol 87*: 430–434, 1972.
105. SNEDDON I: Treatment of steroid-induced rosacea and perioral dermatitis. *Dermatologica 152 suppl 1*: 231–237, 1976.
106. ALANI MD, ALANI SP: Allergic contact dermatitis to corticosteroids. *Ann Allergy 30*: 181, 1972.
107. ARNOLD J, ANTHONIOZ P, MARCHAND JP: Depigmenting action of corticosteroids. Experimental study on guinea pigs. *Dermatologica 151*: 274–280, 1975.
108. BONDI EE, KLIGMAN AM: Adverse effects of topical corticosteroids. *Prog Dermatol 14*: 1–4, 1980.
109. IVE FA, MARKS R: Tinea incognito. *Brit Med J 3*: 149–152, 1968.
110. WISHART J: Norwegian scabies, a Christ Church epidemic. *Australas J Dermatol 13*: 127–131, 1972.
111. HILL CJ, ROSTENBERG A: Adverse effects from topical steroids. *Cutis 21*: 624–632, 1978.
112. KLIGMAN AM, LEYDEN JJ: Adverse effects of fluorinated steroids applied to the face. *JAMA 229*: 60–62, 1974.
113. DEAKIN MJ: Current dangers and problems in the topical use of steroids. *Med J Aust 1*: 120–121, 1976.
114. GOMEZ EC, FROST P: Induction of glycosuria and hyperglycemia by topical corticosteroid therapy. *Arch Dermatol 112*: 1559–1562, 1976.
115. JARRATT MT, SPARK RF, ARNDT KA: The effects of intradermal steroids on the pituitary-adrenal axis and the skin. *J Invest Dermatol 62*: 463–466, 1974.
116. GOLDMAN L: Reactions following intralesional and sublesional injections of corticosteroids. *JAMA 182*: 613–616, 1962.
117. ZAYNOUN ST, SALTI IS: The effect of intracutaneous glucocorticoids on plasma cortisol levels. *Br J Dermatol 88*: 151–156, 1973.
118. MIKHAIL GR, SWEET LC, MELLINGER RC: Parenteral long-acting corticosteroids effect on hypothalamic-pituitary adrenal function. *Ann Allergy 31*: 337–343, 1973.
119. DROSZEZ W, MALUNOWICZ E, LECH BR, et al: Assessment of adreno-cortical function in asthmatic patients on long-term triamcinolone acetonide treatment. *Ann Allergy 42*: 41–43, 1979.
120. ARNOLD HL JR: Comments on "a second point of view." *J Amer Acad Dermatol 5*: 604–605, 1981.
121. PEAKE MD, CLAYTON RM, HOWARD P: Triamcinolone in corticosteroid resistant asthma. *Br J Dis Chest 73*: 39–44, 1979.
122. CAMPBELL TC: Chemical carcinogens and human risk assessment. *Fed Proc 39*: 2467–2484, 1980.
123. DUJOVNE CA, AZARNOFF DC: Clinical complications of corticosteroid therapy. *Med Clin North Am 57*: 1331–1342, 1973.
124. DAVID DS, GRIECE MH, CUSHMAN P JR: Adrenal glucocorticoids after twenty years: A review of their clinically relevant consequences. *J Chron Dis 22*: 637–711, 1970.

125. COLUMB D: Cutaneous manifestations in long-term general cortico-therapy. Study of 100 cases. *Presse Med 79*: 1011–1012, 1971.
126. FLOYD M, MUCKLE TJ, KEW DN: Prednisone-induced leukocytosis in nephrotic syndrome. *Lancet 1*: 1192–1193, 1969.
127. SAVILLE PD, KHARMOSH O: Osteoporosis of rheumatoid arthritis: Influence of age, sex, and corticosteroids. *Arthritis Rheum 10*: 423–430, 1967.
128. KLEIN RG, ARNAUD SB, GALLAGHER JC, et al: Intestinal calcium absorption in exogenous hypercorticism: Role of 25-hydroxyvitamin D and corticosteroid dose. *J Clin Invest 60*: 253–259, 1977.
129. CHESNEY RW, MAZESS RB, HAMSTRA AJ, et al: Reduction of serum 1,25-dihydroxyvitamin D_3 in children receiving glucocorticoids. *Lancet 2*: 1123–1125, 1978.
130. ISAKSON B, LINDHOLM B, CARLGREN G: Cortisone-induced osteoporosis. *Am J Clin Nutr 16*: 287–291, 1965.
131. PINNELL S: Unpublished observation, 1982.
132. SUTTON RD, BENEDECK TG, EDWARDS GA: Aseptic bone necrosis and corticosteroid therapy. *Arch Intern Med 112*: 594–602, 1963.
133. AFIFI AK, BERGMAN RA, HARNEY MC: Steroid myopathy: Clinical, histologic and cytologic observations. *Johns Hopkins Med J 123*: 158–173, 1968.
134. DALE DC, PETERSDORF RG: Corticosteroids and infectious diseases. *Med Clin North Am 57*: 1277–1287, 1973.
135. EAGLSTEIN WH, KATZ R, BROWN JA: The effects of early corticosteroid therapy on the skin eruption and pain of herpes zoster. *JAMA 211*: 1681–1683, 1970.
136. NUSS DD: Herpes zoster: Treatment with high-dose prednisone. *J Assoc Mil Dermatol 5*: 13–15, 1979.